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For Merck, Defense of a Drug Crumbles at a Difficult Time

By BARRY MEIER

For years, evidence mounted that the pain reliever Vioxx might increase the risk of heart attacks or strokes. For years, its maker, Merck, disputed such findings.

A week ago Thursday, Merck's defense started crumbling, with the arrival of irrefutable evidence from one of the company's own studies that Vioxx doubled a long-term patient's chance of having such problems. And yesterday, after a frantic week of internal huddles and meetings with regulators, Merck announced that it would withdraw the drug from the worldwide market.

In many ways, the short but highly profitable history of Vioxx may prove to be a story about the triumph of marketing over science. Even though worrisome evidence began to emerge shortly after the drug's approval five years ago, sales of Vioxx soared to $2.5 billion last year on the strength of one of the biggest direct-to-consumer marketing campaigns yet for a prescription medication. In the first six months of this year alone, Merck spent an estimated $45 million advertising the drug.

Yesterday, some researchers who have long studied the drug said they were surprised, not that Vioxx was being withdrawn but that it had taken so long for the drug's death knell to be sounded.

"It is a terrifying testimony to the power of marketing," said Dr. Jerry Avorn, a divisional director at Brigham and Women's Hospital in Boston.

Signs of Vioxx's risks emerged soon after the Food and Drug Administration approved its sale in 1999 for the treatment of acute pain and chronic pain from arthritis and other problems. The drug, which is known as a COX-2 inhibitor, did not control pain better than older, cheaper drugs. But ulcers and gastrointestinal bleeding occurred less with Vioxx.

But in 2000, Merck submitted a safety study to the F.D.A. showing that patients taking Vioxx faced a significantly higher risk of heart attacks and strokes than patients taking naproxen, a traditional pain reliever. The authors of the study, which was financed by Merck, theorized that the results reflected naproxen's protective effect against heart problems rather than risks posed by Vioxx.

"The investigators and the company came up with a superhypothesis that naproxen was a superdrug for preventing heart attacks," said Dr. Wayne A. Ray, a professor of preventive medicine at Vanderbilt University School of Medicine.

In 2001, the F.D.A. warned Merck that its promotional campaigns for Vioxx were minimizing the cardiovascular risk of the drug and that it was misrepresenting the results of the 2000 study. The next year, the agency required Merck to add language to the drug's label warning about an increased risk of

heart attack and stroke.

By that time, however, investigators like Dr. Ray had begun focusing on Vioxx's safety and the question of whether naproxen, which is sold under the brand name Aleve, helped prevent heart attacks. In studies published in 2002, Dr. Ray and others reported that naproxen did not have a significant protective cardiovascular effect and that Vioxx, when taken at higher dosages that had become common, posed an increased risk of heart-related problems.

The next major scientific finding on Vioxx appeared a year later at a medical meeting where Dr. Avorn and a colleague at Brigham and Women's Hospital, Dr. Daniel H. Solomon, reported on a Merck-financed study, based on a survey of patient records. That survey found that Vioxx, even at some moderate dosages, increased cardiovascular risk.

Merck disputed the findings of the study, and the name of a company epidemiologist who had worked on it was removed from the report before it was published in a medical journal.

In those studies, researchers did not see a similar increase in risk from Celebrex, another COX-2 inhibitor, which is made by Pfizer.

In August, Kaiser Permanente, a large nonprofit health maintenance organization, said that a review of its patient records indicated that those taking Vioxx at dosages greater than 25 milligrams suffered more heart attacks and cardiovascular problems than patients on other medications. An F.D.A. official worked on that report.

Merck officials have long said that the earlier studies, like the Kaiser one, were not definitive because they were surveys based on patient records, rather than a clinical trial in which a drug's effectiveness and side effects are measured against a placebo in real time.

But last week, Merck received bad news from researchers in just such a trial. The test, carefully designed to show if Vioxx was more effective than a placebo in preventing the recurrence of colon polyps, found that the drug increased the risk of heart attack and strokes.

Janet Skidmore, a spokeswoman for Merck, said yesterday that the latest study was the first clinical trial to show such results and the company took immediate action upon receiving data.

But Dr. David Campen, the medical director for drug information, utilization and medical information at Kaiser, said he thought the results of the colon polyp trial were simply another brick in the mounting body of evidence against Vioxx

"I think they made a decision that it was just too risky for them to keep marketing the medication," he said.